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Xamoterol, a β_1-adrenoceptor partial agonist: review of the clinical efficacy in heart failure

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1 Xamoterol (Corwin, Carwin, Corwil, Xamtol, ICI 118,587), a β_1-adrenoceptor partial agonist, improves both systolic and diastolic function in heart failure patients.
2 Double-blind, randomised studies comparing xamoterol with placebo showed that the beneficial haemodynamic effects of xamoterol produced significant improvements in exercise capacity and symptoms in patients with mild to moderate heart failure. These studies formed the basis for a large European multicentre study programme which recruited over 1000 patients, randomised to xamoterol (200 mg twice daily, $n = 617$), digoxin (0.125 mg twice daily, $n = 135$) or placebo ($n = 300$) for 3 months.
3 Efficacy was assessed by measuring exercise capacity and symptoms. The xamoterol group improved exercise capacity by 37% compared with an 18% improvement in the placebo group. Differences in the symptom scores measured by visual analogue scales and Likert scores indicated significant improvements by xamoterol in the cardinal symptoms of heart failure, dyspnoea and fatigue.
4 Analyses of data from subsets of patients in the study showed that elderly patients, patients on no other heart failure therapy and patients with cardiomegaly all had similar improvements in exercise and symptoms to those seen in the whole study population. In the subset which included digoxin treatment, xamoterol produced significantly greater improvements in exercise capacity than digoxin (33% *vs* 17%, $P < 0.05$) and was associated with fewer side-effects.
5 Xamoterol is therefore a promising addition to heart failure therapies currently available.

Keywords xamoterol heart failure partial agonist β_1-adrenoceptor

Introduction

In Western society the incidence of heart failure is high and increases with age. Evidence supporting this comes from the Framingham study which reported an incidence of 2 per 1000 for men and 1 per 1000 for women aged 45–54 years, increasing to 8 per 1000 for men and 7 per 1000 for women aged 65–74 years (Furberg & Yusuf, 1986).

Although a number of mechanisms may be involved in damage to the myocardium, the common end-point is an impairment in myocardial function. This leads to a limitation of exercise tolerance due to dyspnoea and/or fatigue which may be evident during exercise or even at rest. Dyspnoea in patients with heart failure is considered to be due to the pulmonary congestion which results from increased cardiac filling pressures related to impaired diastolic performance. In contrast, the fatigue experienced by these patients is thought to be the result of inadequate perfusion of exercising skeletal muscle (Lipkin & Poole-Wilson, 1986). The symptoms of heart failure are associated with identifiable changes in systolic and diastolic performance and the relevance of diastolic dysfunction has

been emphasised (Grossman & Barry, 1980; Katz & Smith, 1982). It has recently been shown that over 40% of patients with diagnosed heart failure may have normal left ventricular systolic function (Soufer *et al.*, 1985). In such patients, the dominant haemodynamic feature is an abnormal pressure-volume relationship during diastole. The results of this study suggest that impaired systolic function alone does not appear to exist as a cause of heart failure, the remaining 60% of patients having a combination of impaired systolic and diastolic function. If optimal therapy is to be achieved, it is important to recognise the independent contributions of systolic contraction and diastolic relaxation. The need for a therapeutic agent which improves both systolic and diastolic function is apparent.

As a result of impaired cardiac function, compensatory mechanisms act to maintain perfusion of vital organs. These include cardiac hypertrophy and dilatation, activation of the sympathetic nervous system and of the renin-angiotensin system. The endogenous release of neurohormones evolved as an appropriate response to an acute myocardial insult, but these factors appear to be deleterious in chronic heart failure. In this situation, activation of the sympathetic and renin-angiotensin systems increases loading conditions in the failing ventricle and may accelerate progression of the underlying disease (Packer, 1988). A study in patients with early heart failure has shown that it is the sympathetic nervous system which first becomes activated (Bayliss *et al.*, 1987). It has been postulated that activation of the sympathetic nervous system is a marker for heart failure and may contribute to the mortality from the syndrome (Cohn *et al.*, 1984).

Diuretics treat the symptoms of heart failure but have little effect on cardiac contractility. In patients with asymptomatic left ventricular dysfunction, they may reduce ejection fraction and increase ventricular volume (Sharpe *et al.*, 1988). In the elderly, diuretics may cause serious hypokalaemia and/or hyponatraemia in about 20% of patients (McLennan, 1988). In contrast, digitalis increases contractility but often causes adverse effects. Angiotensin converting enzyme (ACE) inhibitors have improved symptoms and exercise capacity in long-term studies (The Captopril-Digoxin Multicentre Research Group, 1988). The ACE inhibitors are effective when added to digitalis and diuretics, but experience in mild heart failure is limited. In addition, they may produce hypotension and renal failure. Furthermore, while ACE inhibitors modify one compensatory mechanism in heart failure, they do not directly affect myocardial contractility. Powerful positive inotropic agents such as dobutamine are useful in the management of acute heart failure but have little clinical application in chronic heart failure.

Thus, currently available agents for increasing myocardial performance are unsatisfactory, although the concept of treating heart failure by directly improving myocardial function is attractive. There is therefore scope for the development of therapeutic agents which improve systolic and diastolic function but which are devoid of the excessive stimulation and other adverse effects of the powerful inotropes. Xamoterol, being a partial agonist, differs significantly from other agents which act on the cardiac β_1-adrenoceptor. As previously noted, the clinical usefulness of full β_1-adrenoceptor agonists which stimulate maximally is limited. Full antagonists, on the other hand, may significantly reduce cardiac output, increase ventricular filling pressure and increase peripheral vascular resistance. As a β_1-partial adrenoceptor agonist, xamoterol occupies the cardiac β-adrenoceptor and stimulates to approximately half the level of a full agonist (Nuttall & Snow, 1982). This provides an appropriate balance between a constant level of mild agonist activity at rest and during exercise, thereby supporting myocardial performance, and protecting the failing heart from an excessive stimulatory cardiac response, e.g. tachycardia, when the sympathetic tone is high, as during maximum exercise.

Haemodynamic effects

Haemodynamic measurements in heart failure patients undergoing cardiac catheterisation procedures have demonstrated that xamoterol improved ventricular contractility and relaxation. In 14 patients with left ventricular dysfunction following myocardial infarction, intravenous xamoterol improved contractility, as shown by increases in dP/dt_{max}, and global diastolic performance as shown by an acceleration of isovolumic relaxation and reduction of mean diastolic wall stress. Interestingly, the ejection fraction of the abnormally contracting ventricular segments appeared to be selectively improved. In a second part of the same study, measurements of myocardial metabolism in 11 patients revealed that myocardial oxygen consumption was unaffected by xamoterol, in spite of the increased contractility, possibly because any increased oxygen demand was offset by the improved relaxation and reduced diastolic wall stress which is an important determinant of myocardial perfusion (Rousseau *et al.*, 1983).

Beneficial changes in diastolic function in patients with previous myocardial infarction were also observed after long-term administration of xamoterol (n = 14, 200 mg twice daily for 3 months) compared with placebo (n = 8); left ventricular pressure and mean diastolic wall stress were significantly decreased by xamoterol compared with placebo. These changes were associated with a downward shift in the diastolic pressure-volume relationship, suggesting that the decreased myocardial stiffness led to improved ventricular distensibility and compliance. The overall result was a favourable influence on the ventricular remodelling process following myocardial infarction. Furthermore, myocardial oxygen demand was unchanged by xamoterol and myocardial lactate extraction tended to improve, indicating a beneficial influence on myocardial metabolism (Pouleur *et al.*, 1988).

Haemodynamic studies have also been performed in patients with heart failure of non-ischaemic aetiology. In 10 patients with idiopathic congestive cardiomyopathy (New York Heart Association [NYHA] Class II, n = 4; Class III, n = 5; Class IV, n = 1), intravenous administration of xamoterol improved left ventricular systolic and diastolic performance as evidenced by increases in dP/dt_{max} and cardiac index at a decreased ventricular filling pressure (Simonsen, 1984). In 12 patients with idiopathic dilated cardiomyopathy (NYHA Class III), an intravenous dose of xamoterol increased contractility (dP/dt_{max} increased from 888 to 1086 mm Hg s^{-1}) and relaxation (negative dP/dt_{max} increased from 1051 to 1269 mm Hg s^{-1}); these beneficial effects resulted in an increased cardiac index (2.0 to 2.4 l min^{-1} m^{-2}), increased ejection fraction (27 to 31%) and decreased ventricular filling pressure (20 to 16 mm Hg) without change in heart rate or myocardial oxygen consumption (Amende *et al.*, 1985). A cautionary note was sounded as in each study one patient with severely compromised left ventricular function showed a negative inotropic response with decreased contractility, cardiac output and heart rate. A lack of positive inotropic response was also seen in nine patients with severe refractory heart failure and high circulating noradrenaline levels (Bhatia *et al.*, 1986). It is postulated that these patients all had increased reflex sympathetic activity and the stimulatory effect of the raised levels of endogenous noradrenaline exceeded the partial agonist activity of xamoterol with the result that the cardiac response was decreased. Supporting evidence for this explanation was obtained from a study in which the haemodynamic effects of xamoterol during exercise were correlated with changes in plasma noradrenaline. It was found that when levels of noradrenaline exceeded 400 to 500 pg ml^{-1}, the endogenous sympathetic activity was greater than that of the partial agonist activity of xamoterol (Sato *et al.*, 1987). In view of these findings, the clinical study programme concentrated on patients in mild to moderate heart failure (NYHA Class II–III) who, in any case, form the large majority of heart failure patients in clinical practice. One interesting finding was that in patients with angina pectoris, the abnormal increase in pulmonary wedge pressure during exercise was consistently decreased, even at maximum exercise when the heart rate was also decreased. These changes were associated with a decreased ST-segment depression and increased exercise work (Detry *et al.*, 1984). It was therefore suggested that xamoterol should be particularly effective in patients with heart failure resulting from ischaemic heart disease (Molajo *et al.*, 1987).

Clinical efficacy studies

The studies described above demonstrated that beneficial haemodynamic effects were produced by xamoterol in patients with mild to moderate (NYHA Class II–III) heart failure. A programme of placebo-controlled studies was therefore initiated in relatively small numbers of patients to establish whether these haemodynamic improvements were translated into clinical benefit when xamoterol was given for periods of up to 3 months. Clinical benefit was assessed by exercise testing and questions about symptoms of dyspnoea and fatigue.

In a single-blind study of 10 patients with dyspnoea on effort and left ventricular dysfunction, with a mean ejection fraction of 28% (range 15–35%), the effects of xamoterol 200 mg twice daily for 2 weeks, followed by placebo for 2 weeks and finally xamoterol for 4 weeks, were compared. All patients were on diuretic treatment with frusemide at a dose of at least 80 mg daily. Xamoterol produced a 28% increase in effort tolerance ($P < 0.05$) at a lower maximum exercise heart rate; exercise duration was unchanged in three patients who had the lowest ejection fractions. Haemodynamic measurements before and after the first dose showed that xamoterol produced an increase in stroke volume index from 40 ± 3 to 46 ± 3 ml $beats^{-1}$ m^{-2} ($P < 0.005$) and a decrease in pulmonary wedge pressure from 14 ± 2 to 10 ± 2 mm Hg ($P < 0.01$) (Molajo & Bennett, 1985).

A double-blind, crossover study comparing xamoterol 200 mg twice daily for 2 weeks and placebo was performed in 15 patients with

NYHA Class II–III heart failure (mean ejection fraction 38%, range 14–61%) consequent upon ischaemic heart disease. Compared with placebo, xamoterol significantly increased exercise duration (284 ± 33 *vs* 361 ± 44 s, $P < 0.01$) and this was associated with a reduction in maximum exercise tachycardia (133 ± 5 *vs* 155 ± 3 beats min^{-1}, $P < 0.001$). Two patients were withdrawn for reasons unrelated to therapy and, of the remaining 13, nine experienced symptomatic improvement while four were unchanged by xamoterol. Twelve patients continued open treatment for up to 20 months with clinical benefit (Beatt *et al.*, 1985).

Improved effort tolerance, symptoms and resting ejection fraction were produced by xamoterol treatment in a double-blind, cross-over comparison with placebo when each treatment was administered to 21 heart failure patients (NYHA Class II–III) for 1 month. Exercise duration was increased by xamoterol (481 ± 37 *vs* 442 ± 283 s, $P < 0.01$) and this was achieved at a lower heart rate (111 ± 3 *vs* 130 ± 4 beats min^{-1}, $P < 0.001$). These beneficial changes were associated with an improvement in resting ejection fraction (47 ± 3 *vs* 42 ± 3%, $P < 0.025$) and symptoms of dyspnoea as measured by visual analogue scale (Vigholt *et al.*, 1987).

A study in patients with mild to moderate heart failure after myocardial infarction provided further evidence of clinical and haemodynamic improvements (Rousseau *et al.*, 1984). A between-group comparison of xamoterol and placebo showed that eight patients treated with xamoterol improved exercise capacity (120 to 154 Watts, $P < 0.05$) and resting haemodynamics (15% reduction in cardiac volumes, 30% reduction in left ventricular end-diastolic pressure, both $P < 0.05$) compared with a placebo group which showed no significant changes.

The overwhelming majority of patients reported in the above studies had heart failure as a consequence of ischaemic heart disease reflecting the fact that this is the major cause of heart failure in the Western world. The known anti-ischaemic properties of xamoterol and the reduction of an inappropriately high tachycardia during exercise could, in part, account for the improved effort tolerance in these patients. Nevertheless, it is evident that the mild positive inotropic effect, resulting in a reduction in ventricular filling pressure and an increase in stroke volume, also plays a role because xamoterol has been shown to be effective in treating heart failure of non-ischaemic aetiology. In a group of 10 patients with idiopathic dilated cardiomyopathy (NYHA Class II–III), treatment with xamoterol for 3 months resulted in improvements in effort tolerance (252 ± 138 to 384 ± 156 s, $P < 0.01$), echocardiographic ejection fraction (29 ± 12 to 39 ± 14%, $P < 0.01$), radionuclide ejection fraction (34 ± 11 to 45 ± 14%, $P < 0.001$) and exercise pulmonary wedge pressure (32 ± 12 to 22 ± 9 mm Hg, $P < 0.05$). Also of interest in this study was the observation that in three patients with plasma noradrenaline levels exceeding 600 pg ml^{-1}, there was a decrease in these levels after xamoterol treatment (Watanabe *et al.*, 1986).

The accumulated evidence from these studies for the efficacy of xamoterol, and its lack of significant side-effects, provided the basis for studies in larger numbers of patients. One of the objectives of this final phase of pre-registration studies was to reproduce as closely as possible selection criteria for patients which would mirror the clinical criteria by which physicians would prescribe xamoterol when it became available for general use. Mild to moderate heart failure patients are generally managed by family doctors or the non-academic hospital where sophisticated technological equipment is generally unavailable and the diagnosis depends on clinical judgement. Thus it was decided that selection criteria for entering patients into the final phase of studies would be based on the same clinical criteria (functional capacity according to the NYHA, based on symptoms and limitation of activity) as those used in the smaller preliminary haemodynamic and efficacy studies described above; it was assumed that the patients in the large studies would therefore have similar haemodynamic derangements.

In excess of 1000 patients were entered into a European multicentre study programme with 3-month treatment periods of either xamoterol or placebo using a double-blind, between group comparison. The basic protocol allowed variations in the exercise methodology (modified Balke treadmill protocol or a bicycle ergometer using 20 Watt min^{-1} increments) and in the use of a positive control group (digoxin 0.125 mg twice daily) to allow for national preferences. Patients were allowed to be on no other treatment or on diuretics, up to 80 mg frusemide daily, and/or nitrates, provided that any concurrent treatment was kept constant throughout the study period. Efficacy was assessed in terms of exercise capacity (exercise duration from the two protocols was converted into exercise work, expressed as kilojoules [kJ], to allow the data to be analysed together), symptoms of heart failure and performance of everyday activities. Changes in symptoms and daily activities were measured by means of 100 mm visual analogue scales (VAS) or 4–5 point Likert scales. Responses to

Likert questionnaires were combined to give a composite measure of 'life values', a term which is defined as the ability of patients to participate in those aspects of life which they value as a result of improved symptoms and ease of activities caused by the heart failure therapy. Measurements of efficacy were made at baseline after a single-blind placebo run-in (1 week) and after the double-blind treatment period (3 months). In order to allow for any differences in baseline values between the treatment groups, an analysis of covariance was performed.

The number of patients randomised to the three treatments were xamoterol 617, placebo 300 and digoxin 135. Most patients (70%) were in mild heart failure NYHA Class II. The most common cause of heart failure was ischaemic heart disease (79%) while other causes included hypertension, cardiomyopathy and non-obstructive valvular disease. Patients were either untreated or on diuretics (45%) and/or nitrates (32%) during the study. The predominant symptoms reported by patients were dyspnoea (94%) and fatigue (76%), while angina pectoris (54%) and peripheral oedema (26%) were reported less frequently. The baseline exercise capacity of the patients, whose mean age was 62 years, was approximately one-third (18 *vs* 53 kJ) that of an aged-matched normal population based on calculations from published data (Astrand & Rodahl, 1977); this provides supporting evidence for the clinical diagnosis of heart failure.

Analysis of the whole data base, involving 617 patients randomised to xamoterol and 300 to placebo, showed that xamoterol produced greater improvements in effort tolerance (37% *vs* 18%, $P < 0.0001$), dyspnoea and fatigue measured by the VAS ($P < 0.0001$ and $P < 0.01$, respectively) and life values ($P < 0.0001$) compared with placebo (Figure 1) (Blackwood & Marlow, 1988). Resting heart rate was not significantly affected by xamoterol but the maximum exercise tachycardia was significantly attenuated (118 *vs* 130 beats min^{-1}, $P < 0.0001$). This large data base permitted the data from four different subsets of patients to be analysed, each subset consisting of at least 250 patients. These subset analyses showed a consistent pattern of responses when xamoterol and placebo were compared.

Heart failure is more common in elderly patients and therefore the data from a subset of patients aged over 65 years (xamoterol $n = 200$, placebo $n = 115$) were examined. Xamoterol produced significantly greater improvements in exercise capacity than placebo (27% *vs* 8%, $P < 0.05$) and in dyspnoea ($P < 0.05$) as measured by VAS. Regression analysis of the exercise data showed an expected reduction in exercise capacity with age and a difference between males and females. The regression analysis also showed the benefit of xamoterol on effort tolerance was such that, after xamoterol treatment, the exercise capacity of a 70-year-old man was equivalent to that of a 62-year-old man treated with placebo (Wray *et al.*, 1988).

In order to answer the question as to whether xamoterol can be used as a sole therapy, data from a subset of patients treated with xamoterol ($n = 290$) or placebo ($n = 135$), and who were on no other therapy, were analysed. Xamoterol produced a significantly greater improvement (28%, $P < 0.0002$) in exercise capacity compared with placebo, as well as improvements in dyspnoea, measured on the VAS ($P < 0.0015$), and in life values ($P < 0.01$). The data provided evidence that xamoterol used as sole initial

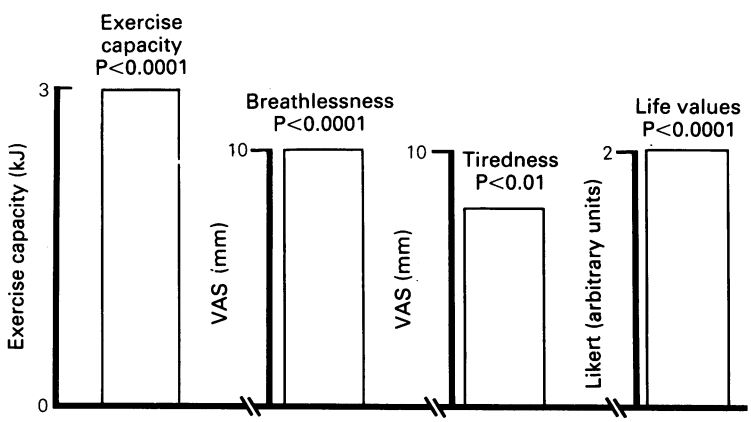

Figure 1 Difference between placebo and xamoterol (200 mg twice daily) in 917 patients in a 3 month, double-blind, randomised study.

therapy is effective in heart failure (Timewell *et al.*, 1988).

A consistent finding in the xamoterol studies has been the attenuation of the exercise tachycardia due to antagonism of the high levels of catecholamines released in response to increased sympathetic drive. This fact, together with the known anti-anginal properties of xamoterol (Detry *et al.*, 1984), has led to speculation that the therapeutic efficacy of xamoterol in improving exercise capacity is due to the anti-ischaemic effect associated with β-adrenoceptor blocking activity (Editorial, 1988). While these properties of xamoterol are advantageous in patients with heart failure resulting from ischaemic heart disease, they cannot account for the improved haemodynamics (systolic and diastolic function) and the clinical benefit seen in patients with non-ischaemic idiopathic cardiomyopathy (Watanabe *et al.*, 1986) or in a subset of 269 patients from the large multicentre study programme. These patients had cardiomegaly (cardiothoracic ratio > 0.52) and their exercise capacity was not limited by angina pectoris, i.e. they stopped exercising because of dyspnoea and/or fatigue only. In the xamoterol-treated patients ($n = 184$) the increase in exercise work (2.8 kJ, $P < 0.02$) over and above that seen in the placebo group ($n = 85$) was comparable to that seen in the whole data base (Franciosa & Marlow, 1987).

In one subset of patients ($n = 433$) studied in Germany and Austria, a positive control (digoxin, 0.125 mg twice daily) was included as a third treatment group (The German and Austrian Xamoterol Study Group, 1988). Treatment with xamoterol ($n = 220$) produced significantly greater clinical benefit than either digoxin ($n = 104$) or placebo ($n = 109$). In the xamoterol group, exercise capacity increased by 33% compared with a 17% increase in the digoxin group ($P < 0.05$) and 5% in the placebo group ($P < 0.001$); the difference between digoxin and placebo did not achieve statistical significance ($P = 0.08$). Significant improvements in symptoms were produced by xamoterol compared with placebo as measured by the VAS; dyspnoea 22 ± 3 mm *vs* 8 ± 4 mm, fatigue 17 ± 3 *vs* 3 ± 4, palpitations 13 ± 2 *vs* 2 ± 3 and chest pain 13 ± 2 *vs* 1 ± 3 (all $P < 0.01$). Differences between digoxin and placebo were not significant. Both active treatments reduced the physical signs of heart failure. The greater efficacy of xamoterol over digoxin should also be seen in the context of the higher incidence of side-effects reported in the digoxin group, particularly those related to the gastrointestinal system. Criticisms were made about the lack of objective evidence of heart failure in these patients and use of a fixed dose of digoxin which may not have provided adequate therapeutic levels (Kaufmann, 1988; Nicholls & Elborn, 1988). In reply to these criticisms, it was pointed out (Von Olshausen, 1988) that the diagnosis of heart failure and initiation of therapy is usually made on a clinical diagnosis, which was reflected in the pragmatic selection criteria for the study. Dose-titration in any randomised, double-blind, clinical study, presents insurmountable problems in study design and execution. The requirement for digoxin dose-titration underlines the practical difficulty of selecting an appropriate dose in clinical practice. The mean digoxin plasma concentration was nevertheless in the therapeutic range and, even at this level, was associated with an increased incidence of side-effects.

An important feature of the xamoterol efficacy data is the lack of tachyphylaxis. This has been a problem with full agonists, such as pirbuterol, where improvements seen acutely were not maintained on long-term treatment and were associated with β-adrenoceptor down-regulation (Colucci *et al.*, 1981). Studies in the rat have shown that xamoterol does not produce down-regulation of the ventricular β_1-adrenoceptors (Barnett & Maguire, 1986). Haemodynamic improvements produced by xamoterol have been maintained on chronic treatment and clinical efficacy has been demonstrated over an extended period.

Conclusion

Haemodynamic measurements in patients with mild to moderate heart failure have demonstrated that xamoterol produced significant improvements in systolic and diastolic performance. Efficacy studies involving relatively small numbers of patients with a clinical diagnosis of mild to moderate heart failure confirmed by haemodynamic measurements showed that the haemodynamic derangements were improved by xamoterol and were accompanied by an increased exercise capacity and relief of symptoms. Using the same clinical diagnostic criteria for selection of patients, a large multicentre study programme involving over 1000 patients provided confirmatory evidence that treatment with xamoterol was of clinical benefit by improving effort tolerance, symptoms and signs of heart failure. Analysis of data from subsets of these patients showed a consistent pattern of beneficial responses to xamoterol in, for example, the elderly and in patients in whom xamoterol was the sole therapy. Tachyphylaxis has not been observed since haemodynamic improvements

and clinical benefit have been maintained on chronic dosing. The results provide evidence that xamoterol is a promising addition to the currently available treatment for heart failure.

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